

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification :

Not classified

A2

(11) International Publication Number:

WO 00/45627

(43) International Publication Date:

10 August 2000 (10.08.00)

(21) International Application Number: PCT/US00/02372

(22) International Filing Date: 31 January 2000 (31.01.00)

(30) Priority Data:

09/244,348

4 February 1999 (04.02.99)

US

(71) Applicant: MOBETA, INC. [US/US]; 670 San Antonio Road,
Los Altos, CA 94022 (US).

(72) Inventors: DELFINO, Michelangelo; 670 San Antonio Road,
Los Altos, CA 94022 (US). DAY, Mary, Elizabeth; 670
San Antonio Road, Los Altos, CA 94022 (US).

(74) Agents: DATE, Vandana et al.; Robins & Associates, Suite
200, 90 Middlefield Road, Menlo Park, CA 94025 (US).

(81) Designated States: BR, CA, JP, European patent (AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE).

Published

*Without international search report and to be republished
upon receipt of that report.*

(54) Title: RADIOACTIVE TRANSITION METAL STENTS

(57) Abstract

A radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal stent surface is chemically bound to a radioactive material; and a method for producing the radioactive transition metal stent wherein the radioisotope is chemically bound to, and is uniformly confined to the transition metal stent surface without affecting the metallurgical properties of the transition metal stent is disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

RADIOACTIVE TRANSITION METAL STENTS

5

Technical Field

This invention relates generally to intravascular implantation devices and more particularly to a radioactive transition metal stent, wherein the stent surface comprises chemically-bound radioisotope, for therapeutic and diagnostic
10 applications.

Background of the Invention

Intravascular stents have been permanently implanted in coronary or peripheral vessels to prevent restenosis. See, e.g. U.S. Patent Nos. 5,800,507;
15 5,059,166 and 5,840,009. Trauma or injury to the artery caused by angioplasty procedures, implantation of stents, atherectomy or laser treatment of the artery, result in restenosis, i.e., the closure or renarrowing of the artery. Restenosis, a natural healing reaction to the injury of the arterial wall, begins with the clotting of blood at the site of the injury, followed by intimal hyperplasia, i.e. the rapid
20 growth of the injured arterial tissue through the openings in the stent, and the migration and proliferation of medial smooth muscle cells, until the artery is again stenotic or occluded.

However, such stents are not always effective in preventing restenosis and can cause undesirable local thrombosis. A variety of solutions have been
25 proposed to minimize these undesirable effects, such as coating the stents with a biocompatible or an anti-thrombotic surface, wherein the stent-surface is seeded with endothelial cells or fibrin, or using stents as drug delivery devices. See for example, U. S. Patent Nos. 5,800,507; 5,059,166; WO 91/12779 and WO 90/13332.

30 Implanted stents, in conjunction with endovascular irradiation, are believed to prevent restenosis by alleviating neointimal hyperplasia. The beta-particle emitter, phosphorus-32 (³²P) radioisotope, has been used as a permanent

medical implant. Fischell et al. describe stents formed from radioactive materials, wherein a radioisotope is incorporated into the stent by physical methods, such as coating, plating, implanting on the exterior surface of the stent; inserting inside the stent; and alloying into the metal from which the stent is made. Alternatively, a beam of an ionized radioisotope is directed on the surface of the stent. See U.S. Patent Nos. 5,059,166, 5,176,617, 5,722,984, and 5,840,009. Typically, an ion-implantation method requires irradiating sublimed red phosphorous (to avoid contamination) for about ten days to achieve a sufficient concentration of phosphorous-32 (^{32}P) to obtain radioactivity of 4 to 13 μCi per stent. However, this method is expensive, requires sophisticated equipment, and the transfer of the radioactive source from the nuclear reactor to the ion-implanter to the medical site adversely affect the short half-life of phosphorous-32 (^{32}P) (14.3 days). Additionally, ion-implantation damages the surface of the stent, the interstitially implanted phosphorous-32 (^{32}P) diffuses rapidly and is relatively unstable compared to chemically bound phosphorous-32 (^{32}P). Moreover, ion-implantation requires beam and/or substrate scanning to achieve uniformity, which is difficult to obtain on a radial open-mesh stent. Thus conventional methods result in lower quality, non-uniform radioactive stents.

Strathearn, et al. describe a process for diffusing chemically bound radioactive ions below the surface of the substrate, wherein diffusion is accomplished by heating the substrate between 300° to 600°C (U.S. Patent No. 5,851,315). However, current techniques do not provide for radioactive stents with a radioisotope concentrated at the point of maximum tissue penetration, wherein the radioisotope, such as phosphorus-32 (^{32}P), is chemically bound to and is uniformly confined to the surface without affecting the metallurgical properties, such as ductility and malleability, of the stent. Thus, there is a need for improved and cost-effective radioactive stents, wherein the radioisotope is uniformly distributed over the surface and is concentrated at the point of maximum tissue penetration.

Summary of the Invention

The present invention relates to a radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal surface is chemically bound to a radioactive material; and a method of producing the radioactive transition metal stent wherein the radioisotope is chemically bound to and is uniformly confined to the transition metal surface without affecting the metallurgical properties of the stent. Unlike conventional methods, the present method does not rely on the complex techniques described above. Accordingly, the present invention provides an improved and cost-effective radioactive transition metal metaphosphate stent surface and a method of making the same.

In one aspect, the invention relates to a radioactive transition metal stent comprising one or more transition metals, wherein the transition metal surface is chemically bound to a radioactive material, and further wherein the transition metal is a single element or an alloy of two or more transition metals. In a preferred embodiment, the radioactive material comprises a phosphorus-32 (^{32}P) metaphosphate, wherein the radioactivity of the transition metal stent ranges from about 0.1 μCi to about 100 μCi per stent.

In another aspect, the invention relates to a method of producing a radioactive transition metal stent, comprising one or more transition metals wherein the transition metal surface is chemically bound to a radioactive material, comprising:

- (i) providing a solution of dehydrated phosphorus-32 (^{32}P) enriched metaphosphoric acid;
- (ii) mixing the phosphorus-32 (^{32}P) enriched metaphosphoric acid with a inert polymer to form an emulsion;
- (iii) stabilizing the emulsion;
- (iv) immersing a transition metal stent in the stabilized emulsion;
- (v) removing the stent from the emulsion; and
- (vi) washing and drying the stent to obtain the radioactive transition metal metaphosphate stent.

In an alternative embodiment, the stent is further immersed in a suitable non-polar solvent with a low dielectric constant, such as n-hexane, chloroform,

carbon tetrachloride, diethyl ether, and the like, to remove the residual polymer. In a preferred embodiment, the non-polar solvent is n-hexane.

In preferred embodiments, the transition metal is a single element or an alloy of two or more transition metals and the inert polymer is a polysiloxane polymer. In another preferred embodiment, the phosphorus-32 (^{32}P) enriched metaphosphoric acid has a radioactivity of about 1 mCi to about 10,000 mCi per ml and is mixed with a linear polysiloxane polymer to form an emulsion, wherein the emulsion is stabilized at a temperature between 150°C to about 300°C, and further wherein the stent is immersed in the emulsion for a duration of between about 10 minutes to about 180 minutes to yield a transition metal stent metaphosphate having a radioactivity of about 0.1 μCi to about 100 μCi per stent.

In an alternative embodiment, the transition-metal stent is microscopically roughened prior to immersion or concomitantly in the emulsion. In a preferred embodiment, the transition-metal stent is microscopically roughened in the upper stent surface.

These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

Brief Description of the Drawings

Figure 1 illustrates the X-ray photoelectron spectroscopy (XPS) sputter depth profile for a radioactive stainless steel stent of the invention.

Figure 2 illustrates the binding energy profile for a radioactive stainless steel stent of the invention.

Detailed Description

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of chemistry, biochemistry, and medicine, including diagnostics, which are within the skill of the art. Such techniques are explained fully in the literature. See, e.g., *Principles of Physical Chemistry*, Maron, S.H. and Prutton, C.F., (4th Edition, 1965, The MacMillan Company) and *Advanced Inorganic Chemistry*, Cotton, F.A. and Wilkinson, G., (3rd Edition, 1972, Interscience Publishers).

A. Definitions

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

It must be noted that, as used in this specification and the appended
5 claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a transition metal" includes two or more such metals, and the like.

Unless defined otherwise, all technical and scientific terms used herein
10 have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. The following terms are intended to be defined as indicated below.

As used herein, the terms "transition metal" or "transition element" refers to any element in which the filling of the outermost shell to eight electrons within a periodic table is interrupted to bring the penultimate shell from 8 to 18 or 32
15 electrons. Transition elements include, without limitation, scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, ytterbium, zirconium, niobium, molybdenum, silver, lanthanum, hafnium, tantalum, tungsten, rhenium, rare-earth elements, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium,
20 erbium, thulium, yttrium, lutetium, technetium, rhodium, actinium, thorium, protactinium, uranium, neptunium, plutonium, americium, curium, berkelium, californium, einsteinium, fermium, mendelevium, nobelium and lawrencium.

As used herein, the term "alloy" refers to a mixture of two or more transition metals. Examples of alloys include, but are not limited to, stainless-
25 steel type 316, stainless-steel type 316L, nitinol (a nickel-titanium alloy), elgiloy (a cobalt-nickel alloy), all commercially available from, e.g. Alan Steel & Supply Co., Redwood City, CA; Carpenter Technology Corp., Hayward, CA; Shape Memory Applications, Inc., Santa Clara, CA and Elgiloy Ltd. Partnership, Elgin, IL.

30 As used herein, the term "stent" refers to a metallic surface, wherein the metal may be any geometrical shape or form, such as round, rectangular, square, cylindrical, flat surfaces, catheters, wires, helically coiled spring, and the like. In

a preferred embodiment, the metal may be any material or device used to support a tissue, graft or anastomosis during the healing process. In another preferred embodiment, the stent is in the form of a cylindrical wire.

As used herein, an "inert polymer" refers to a liquid that does not react with the stent metal or the dehydrated phosphorus-32 enriched metaphosphoric acid, and does not cause the soluble phosphorus-32 concentration to be reduced. Examples of inert polymers include, but are not limited to, a linear polysiloxane polymer having a room-temperature kinematic viscosity of 0.1 to 1000 CS, high temperature oils and lubricants having a flash point below 250°C, preferably a flash point of between 190°-250°C, and more preferably between 200°-230°C.

As used herein, the term "kinematic viscosity" is defined as the ratios of viscosity coefficient divided by density. A standard kinematic viscosity unit is a CS.

15 B. General Methods

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular transition metal stents or process parameters as such may, of course, vary. It is also to be understood that the terminology and examples used herein are for the purpose of describing particular embodiments of the invention only, and are not intended to be limiting.

Although a number of transition metal stents and methods similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described.

The invention provides a radioactive transition metal stent and a method of producing the same. Stents for use with the present invention can be of any useful geometrical shape or form, as described above. Generally, stents have a radial area that may be approximated as half that of a cylindrical tube. Thus the surface area of a typical 0.3 cm diameter, 2 cm long stent is approximately 2 cm². The length of the stent will vary depending on the particular application and can be as long as 45 mm and as short as 1.5 mm.

Using currently available techniques, a radioactive doped transition metal metaphosphate stent may be produced as follows. For example, for a 10 nm thick

transition metal metaphosphate containing 20% phosphorous, e.g., $\text{Me}_2(\text{PO}_3)_3$, having a typical density of 5×10^{22} atoms/cm³, there are a total of 1×10^{16} phosphorus atoms/cm². A transition metal metaphosphate grown uniformly on a 2 cm stent as described above, would accommodate 2×10^{16} phosphorus atoms.

5 The radioactive phosphorus atoms must be present in a concentration sufficient to permit efficient transfer of radioactive atoms from an appropriate chemical source to the stent. For example, the ratio of available phosphorus in 0.5 ml anhydrous orthophosphoric acid (H_3PO_4) to that to be incorporated into the stent is approximately 300,000:1. Thus, 1.0 Ci phosphorus-32 enriched acid will yield a
10 3.3 μCi phosphorus-32 enriched stent.

Uniform and continuous contact with the stent using such a small volume of the very viscous orthophosphoric acid is impractical and not feasible. Thus to obtain a radioactive transition metal stent, wherein the radioisotope is chemically bound to, and is uniformly confined to the transition metal surface without
15 affecting the metallurgical properties of the stent, it is necessary to increase the effective contact area of the stent surface with the orthophosphoric acid, without degrading or reducing the radioactive concentration of the acid. The instant invention provides a method wherein the transition metal stent is in uniform and continuous contact with the radioactive metaphosphoric acid. The radioactively
20 enriched acid is suspended in a suitable emulsion, and the transition metal stent is then immersed in the stabilized emulsion to allow a uniform, surface-controlled metaphosphate growth on the transition metal stent surface. Additionally, more than one radioactive stent can be produced simultaneously using the method of the invention, thus adding to the cost-effectiveness of the radioactive stents.

25 A procedure for producing a radioactive transition metal stent in which the radioisotope is chemically bonded to the transition metal stent surface is described as follows. In preferred embodiments, the transition metal is a single element or an alloy of two or more transition metals and the inert polymer is a polysiloxane polymer.

30 Metaphosphoric acid $(\text{HPO}_3)_n$ (wherein $n=3$ or 4) is prepared according to known procedures. (See The Merck Index, 9th Ed, 1976, page 956). Phosphorus-32 enriched 85% H_3PO_4 is heated in an open vessel at a temperature above 300°C,

preferably about 300°C to about 420°C, and most preferably about 310°C to about 350°C; for approximately about 5 to 50 hours, preferably 20 to 50 hours, and most preferably 20 to 30 hours, to yield the metaphosphoric acid having a radioactivity of about 1 mCi to about 10,000 mCi per ml, preferably 10 mCi to about 7,000 mCi per ml, and more preferably 100 mCi to about 3,000 mCi per ml. An inert polymer is added to the metaphosphoric acid to form an emulsion, wherein the volume ratio of acid to polymer ranges from about 1:1 to about 1:500, preferably from about 1:1 to about 1:300, and most preferably from about 1:2 to about 1:10. The emulsion is then stabilized, i.e. equilibrated, with agitation, at about 150-300°C. A transition metal stent having a thickness of about 10 nm to about 1000 nm, preferably about 10 nm to about 700 nm, and more preferably about 10 nm to about 500 nm, is completely immersed in the emulsion for about 10-120 minutes, preferably 10 to 180 minutes, and most preferably 30 to 60 minutes, while being gently agitated so that it is in constant contact with the acid globules. The stent is then removed from the emulsion, rinsed in boiling deionized water, rinsed again in room temperature deionized water, and dried using nitrogen gas. The stent is then optionally immersed in a suitable non-polar solvent with a low dielectric constant, such as n-hexane, chloroform, carbon tetrachloride, diethyl ether, and the like, to remove the residual polymer.

The radioactivity of the stent is measured using a suitable beta-particle counter and readied for permanent or temporary endovascular implantation, such as coronary, iliac, urethral, biliary stents, and the like. In an alternative embodiment, the radioactive stent may additionally comprise antithrombogenic agents. In one embodiment, the radioactive stent is temporarily placed within the lumen of a vessel, for example a thin wire with a radioactive tip is placed within the bile duct, wherein the wire can be withdrawn after a limited time.

In preferred embodiments, the transition metal stent has a radioactivity of about 0.1 μ Ci to about 100 μ Ci, preferably of about 0.2 μ Ci to about 90 μ Ci, and more preferably of about 0.5 μ Ci to about 80 μ Ci per stent; wherein about 1% to about 67%, preferably about, and more preferably about 1% to about 33% of the total surface comprises chemically bound phosphorus-31 and phosphorus-32

atoms. The chemically-bound phosphorous-32 is incorporated primarily on the surface of the stent, up to a depth of about 300A°, preferably about 200A°, most preferably 100A° from the surface of the stent.

In another embodiment, the transition metal stent is microscopically roughened, using known procedures, prior to immersion in the emulsion. In an alternative embodiment, the transition metal stent is microscopically roughened during immersion in the emulsion. In a preferred embodiment, the transition-metal stent is microscopically roughened in the upper stent surface. For example, the transition metal stent may be roughened by chemically etching the stent either prior to being placed in the emulsion, or the stent may be etched during immersion by the acidic emulsion. Generally, etching with chemicals, such as acid solutions, e.g., HCl solution, causes the surface to pit and roughen.

The following examples are illustrative in nature, and are not intended to limit the scope of the present invention in any manner.

15

Example 1

Metaphosphoric acid $(\text{HPO}_3)_n$ (wherein $n = 3$ or 4) is prepared according to known procedures. (See The Merck Index, 9th Ed, 1976, page 956). Phosphorus-32 enriched 85% H_3PO_4 (0.5ml) is heated in an open vessel at a temperature above 300°C for approximately about 5 to 50 hours to yield the metaphosphoric acid having a radioactivity of about 1 mCi to about 10,000 mCi per ml. Dimethylpolysiloxane polymer (Dow Corning, boiling point > 200°C and a kinematic viscosity of about 20 CS) (20 ml) is added to the metaphosphoric acid to form an emulsion. The emulsion is then stabilized, with agitation, at about 150-200°C. A stent, such as a stainless steel type 316L stent is completely immersed in the emulsion for about 10-120 minutes, while being gently agitated so that it is in constant contact with the acid globules. The stent is then removed from the emulsion, rinsed in boiling deionized water, rinsed again in room temperature deionized water, and dried using nitrogen gas. The stent is then optionally immersed in a suitable non-polar solvent with a low dielectric constant, such as n-hexane, chloroform, carbon tetrachloride, diethyl ether, and the like, to remove the residual polymer.

30

Example 2

Radioactive stainless steel type 316 stents (1.9cm^2) (Alan Steel & Supply Co., Redwood City, CA) were produced according to the procedure described in Example 1 above.

5 Metaphosphoric acid was prepared as follows. Orthophosphoric acid (4.5 ml) was added to a vitreous carbon crucible (3.2 cm diameter, 4.6 cm deep) housed in a temperature controlled copper block heater. A chromel-alumel thermocouple inserted in the copper block was used to monitor the temperature and as a feedback loop for controlling temperature. The copper block was
10 incrementally heated over a period of 45 minutes as follows: the temperature was raised to 153°C in 10 minutes; to 175°C in 20 minutes; to 200°C in 30 minutes; to 210°C in 36 minutes and finally to 330°C in 45 minutes. The copper block was maintained at 330°C for 19 hours, to yield the metaphosphoric acid.

 The temperature of the copper block was lowered to 215°C in 10 minutes.
15 Dimethoxypolysiloxane polymer (Dow Corning 220 fluid, 20 CS kinematic viscosity) (4.9 ml) was then added to the crucible containing the metaphosphoric acid and the emulsion was stabilized at 215°C . The stainless steel type 316 stent was placed in the crucible and stirred periodically for 30 minutes. The stent was removed from the emulsion and placed in a pyrex beaker containing tap water
20 (room temperature). The stent was then rinsed under running tap water and dried. The stent was subsequently dipped in n-hexane to remove any residual polymer.

 Figure 1 illustrates the X-ray photoelectron spectroscopy (XPS) sputter depth profile for a radioactive stainless steel stent, wherein the atomic concentration (%) is plotted against the depth (nm) for the elements, P, Fe, O and
25 Mo. The radioactive stent contains about 20% chemically-bound phosphorous, incorporated primarily on the surface of the stent, up to a depth of approximately 20 nm.

 Figure 2 illustrates the binding energy (eV) for the phosphorous $2p^{3/2}$ core-level transition measured according to standard procedures. As evidenced
30 from figure 2, all of the phosphorous is chemically bound: the peak at 134 eV corresponds to the metaphosphate and the peak at 130 eV corresponds to reduced phosphorous, i.e. phosphide.

Thus, a radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal stent surface is chemically bound to a radioactive material is disclosed. A method for producing the radioactive transition metal stent wherein the radioisotope is chemically bound to, and
5 uniformly confined to the stent surface without affecting the metallurgical properties of the stent is also disclosed. Although preferred embodiments of the invention have been described in some detail, it is understood that obvious variations can be made without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

- 5 1. A radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal stent surface is chemically bound to a radioactive material.
2. The radioactive transition metal stent of claim 1 wherein the
10 transition metal is a single element or an alloy of two or more transition metals.
3. The radioactive transition metal stent of claim 2, wherein the transition metals are selected from a group consisting of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, ytterbium,
15 zirconium, niobium, molybdenum, silver, lanthanum, hafnium, tantalum, tungsten, rhenium, rare-earth elements, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, yttrium, lutetium, technetium, rhodium, actinium, thorium, protactinium, uranium, neptunium, plutonium, americium, curium, berkelium,
20 californium, einsteinium, fermium, mendelevium, nobelium and lawrencium.
4. The radioactive transition metal stent of claim 2, wherein the transition metal is an alloy selected from a group consisting of stainless-steel type 316, stainless-steel type 316L, a nickel-titanium alloy and a cobalt-nickel alloy.
25
5. The radioactive transition metal stent of claim 1 wherein the radioactive material comprises a metaphosphate surface wherein about 1% to about 67% of the total surface comprises chemically bound phosphorus-31 and phosphorus-32 atoms.
30

6. The radioactive transition metal stent of claim 5, wherein the metaphosphate surface comprises a radioactivity of about 0.1 μ Ci to about 100 μ Ci per stent.

5 7. The radioactive transition metal stent of claim 1 wherein the stent has a thickness of about 10 nm to about 1000 nm.

8. A method of producing a radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal stent
10 surface is chemically bound to a radioactive material, comprising:

- (i) providing a solution of dehydrated phosphorus-32 enriched metaphosphoric acid;
- (ii) mixing the phosphorus-32 enriched metaphosphoric acid with an inert polymer to form an emulsion;
- 15 (iii) stabilizing the emulsion;
- (iv) immersing a transition metal stent in the stabilized emulsion;
- (v) removing the stent from the emulsion; and
- (vi) washing and drying the stent to obtain the radioactive transition metal stent.

20

9. The method of claim 8 further comprising immersing the stent from step (vi) in a suitable non-polar solvent with a low dielectric constant to remove the residual polymer.

25 10. The method of claim 9, wherein the non-polar solvent is hexane.

11. The method of claim 8 wherein the transition metal stent comprises one or more transition metals.

30 12. The method of claim 11, wherein the transition metal is a single element or an alloy of two or more transition metals.

13. The method of claim 11, wherein the transition metals are selected from a group consisting of scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, ytterbium, zirconium, niobium, molybdenum, silver, lanthanum, hafnium, tantalum, tungsten, rhenium, rare-earth elements, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, yttrium, lutetium, technetium, rhodium, actinium, thorium, protactinium, uranium, neptunium, plutonium, americium, curium, berkelium, californium, einsteinium, fermium, mendelevium, nobelium and lawrencium.
14. The method of claim 11, wherein the transition metal is an alloy selected from a group consisting of stainless-steel type 316, stainless-steel type 316L, a nickel-titanium alloy and a cobalt-nickel alloy.
15. The method of claim 8, where the volume ratio of dehydrated metaphosphoric acid to inert polymer ranges from about 1:1 to about 1:500.
16. The method of claim 8, where the phosphorus-32 enriched metaphosphoric acid in step (ii) has a radioactivity of about 1 mCi to about 10,000 mCi per ml.
17. The method of claim 8, wherein the inert polymer is a linear polysiloxane polymer having a room-temperature kinematic viscosity of about 0.1 to about 1000 CS.
18. The method of claim 8, wherein in step (iii) the emulsion is stabilized at a temperature between 150°C to about 300°C.
19. The method of claim 8, wherein in step (iv) the transition metal stent is immersed in the emulsion for a duration of between about 10 minutes to about 180 minutes.

20. The method of claim 8, wherein the radioactive transition metal stent comprises a radioactivity of about 0.1 μCi to about 100 μCi per stent.

21. The method of claim 8, wherein the transition metal stent is
5 microscopically roughened.

22. The method of claim 21, wherein the transition metal stent is microscopically roughened prior to immersion in the emulsion.

10 23. The method of claim 21, wherein the transition metal stent is microscopically roughened concomitantly in the emulsion.

24. The method of claim 21, where the transition metal stent is microscopically roughened in the upper stent surface.
15

25. A radioactive transition metal stent produced by the method of claim 8.

26. A radioactive transition metal stent produced by the method of
20 claim 9.

27. A radioactive transition metal stent produced by the method of claim 21.

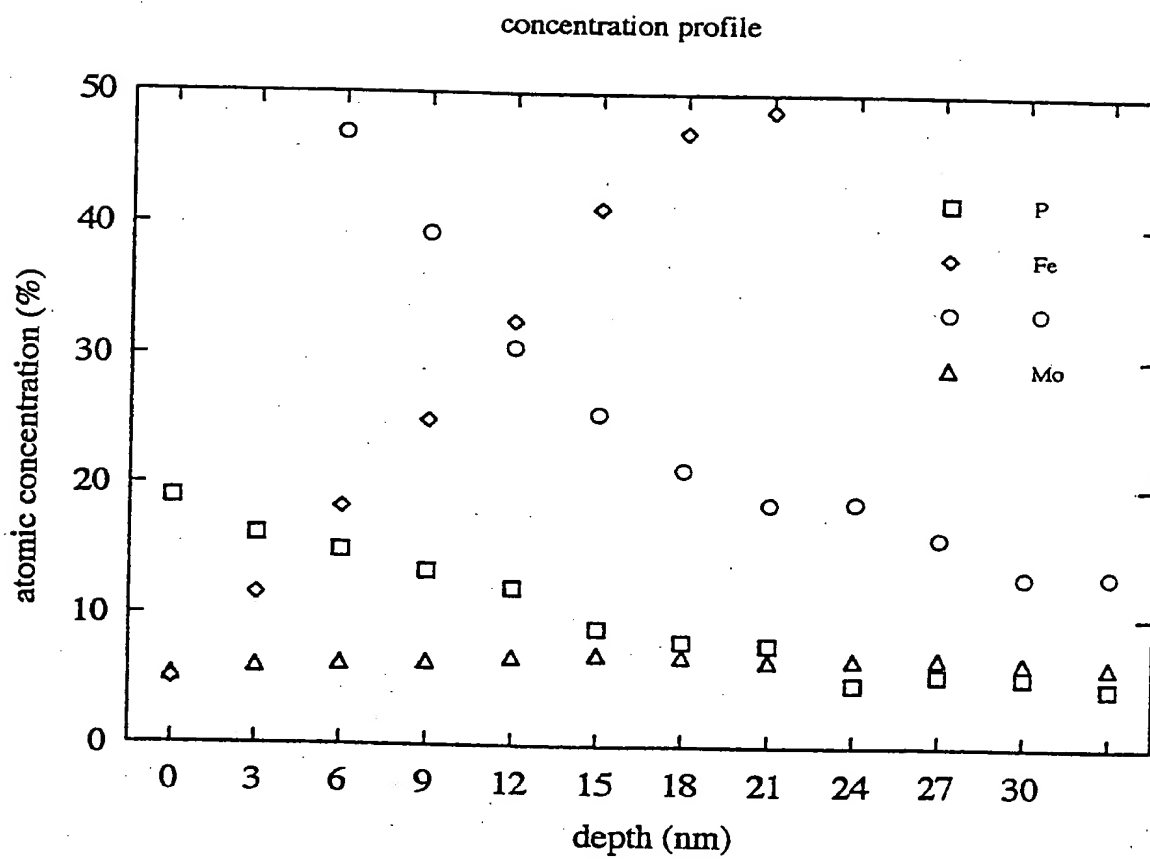


FIG. 1

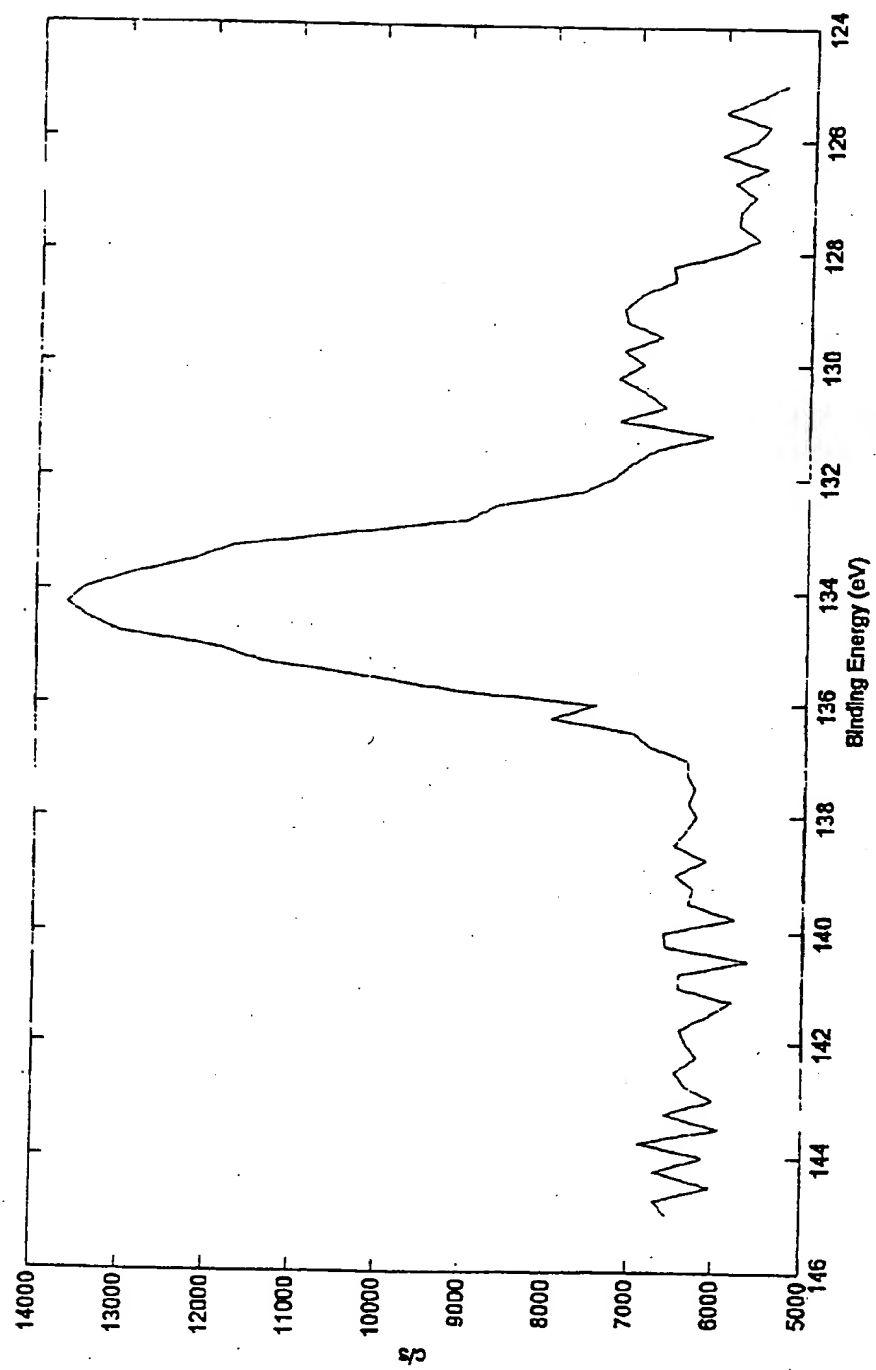


FIG. 2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 August 2000 (10.08.2000)

PCT

(10) International Publication Number
WO 00/45627 A3

- (51) International Patent Classification⁷: A61N 5/00 (74) Agents: DATE, Vandana et al.; Robins & Associates, Suite 200, 90 Middlefield Road, Menlo Park, CA 94025 (US).
- (21) International Application Number: PCT/US00/02372
- (22) International Filing Date: 31 January 2000 (31.01.2000) (81) Designated States (*national*): BR, CA, JP.
- (25) Filing Language: English (84) Designated States (*regional*): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
- (26) Publication Language: English
- (30) Priority Data: 09/244,348 4 February 1999 (04.02.1999) US Published: — With international search report.
- (71) Applicant: MOBETA, INC. [US/US]; 670 San Antonio Road, Los Altos, CA 94022 (US). (88) Date of publication of the international search report: 14 December 2000
- (72) Inventors: DELFINO, Michelangelo; 670 San Antonio Road, Los Altos, CA 94022 (US). DAY, Mary, Elizabeth; 670 San Antonio Road, Los Altos, CA 94022 (US). For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/45627 A3

(54) Title: RADIOACTIVE TRANSITION METAL STENTS

(57) Abstract: A radioactive transition metal stent, comprising one or more transition metals, wherein the transition metal stent surface is chemically bound to a radioactive material; and a method for producing the radioactive transition metal stent wherein the radioisotope is chemically bound to, and is uniformly confined to the transition metal stent surface without affecting the metallurgical properties of the transition metal stent is disclosed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02372**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61N 5/00

US CL : 600/1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/1-3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST

Search Terms: stent, radioactive, transition metal, transition, metal, radioactive transition metal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X,P | US 5,919,126 A (ARMINI) 06 July 1999, cols. 4 and 5. | 1-3, 6 |
| Y,P | | 4, 5 |
| Y | US 5,674,177 A (HEHRLEIN et al.) 07 October 1997, col. 3. | 4, 5 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | |
|--|---|--|
| * Special categories of cited documents: | T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | X | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | Y | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | A | document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | | |
| *P* document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

27 MARCH 2000

Date of mailing of the international search report

07 JUN 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized Officer

BRIAN SZMAL

Telephone No. (703) 308-3737

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02372

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02372

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-7, drawn to a radioactive transition metal stent.

Group II, claims 8-27, drawn to a method of producing a radioactive transition metal stent.

Groups I and II, the inventions listed as these groups do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The method of manufacture of the stent could also be used to manufacture guide wires or other implanted devices, utilizing a radioactive transition metal.